

## **MESNA - mesna injection, solution**

Amerinet Choice

### **DESCRIPTION**

Mesna Injection is a detoxifying agent to inhibit the hemorrhagic cystitis induced by ifosfamide. The active ingredient mesna is a synthetic sulfhydryl compound designated as sodium-2-mercaptoethane sulfonate with a molecular formula of  $C_2H_5NaO_3S_2$  and a molecular weight of 164.18. Its structural formula is as follows:



Mesna Injection is a sterile, nonpyrogenic, aqueous solution of clear and colorless to light pink appearance in clear glass multidose vials for intravenous administration. Mesna Injection contains 100 mg/mL mesna, 0.25 mg/mL edetate disodium and sodium hydroxide and/or hydrochloric acid for pH adjustment. Mesna Injection multidose vials also contain 10.4 mg of benzyl alcohol as a preservative. The solution has a pH range of 6.5 to 7.3.

### **CLINICAL PHARMACOLOGY**

#### **Mechanism of Action**

Mesna was developed as a prophylactic agent to reduce the risk of hemorrhagic cystitis induced by ifosfamide.

Analogous to the physiological cysteine-cystine system, mesna is rapidly oxidized to its major metabolite, mesna disulfide (dimesna). Mesna disulfide remains in the intravascular compartment and is rapidly eliminated by the kidneys.

In the kidney, the mesna disulfide is reduced to the free thiol compound, mesna, which reacts chemically with the urotoxic ifosfamide metabolites (acrolein and 4-hydroxy-ifosfamide) resulting in their detoxification. The first step in the detoxification process is the binding of mesna to 4-hydroxy-ifosfamide forming a nonurotoxic 4-sulfoethylthioifosfamide. Mesna also binds to the double bonds of acrolein and other urotoxic metabolites.

In multiple human xenograft or rodent tumor model studies of limited scope, using IV or IP routes of administration, mesna in combination with ifosfamide (at dose ratios of up to 20-fold as single or multiple courses) failed to demonstrate interference with antitumor efficacy.

#### **Pharmacokinetics**

At doses of 2 to 4 g/m<sup>2</sup>, the terminal elimination half-life of ifosfamide is about 4 to 8 hours. As a result, in order to maintain adequate levels of mesna in the urinary bladder during the course of elimination of the urotoxic ifosfamide metabolites, repeated doses of mesna are required.

#### **IV-IV-IV Regimen**

After intravenous administration of an 800 mg dose, the half-lives of mesna and dimesna in the blood are 0.36 hours and 1.17 hours, respectively. Approximately 32% and 33% of the administered dose was eliminated in the urine in 24 hours as mesna and dimesna, respectively. The majority of the dose recovered was eliminated within 4 hours. Mesna has a plasma clearance of 1.23 L/h/kg.

#### **Special Populations**

##### **Gender Effect**

An analysis was conducted in four males and four female volunteers; no differences in plasma pharmacokinetics were detected.

##### **Pediatrics and Geriatrics**

Pharmacokinetic data of mesna in pediatric and geriatric patients are not available.

##### **Hepatic and Renal Insufficiency**

No clinical studies were conducted to evaluate the effect of hepatic impairment or renal impairment on the pharmacokinetics of mesna.

##### **Drug-Drug Interaction**

No clinical drug interaction studies have been conducted with mesna.

#### **Clinical Studies**

##### **IV Mesna**

Hemorrhagic cystitis produced by ifosfamide is dose dependent (Table 1). At a dose of 1.2 g/m<sup>2</sup>, ifosfamide administered daily for 5 days, 16 to 26% of the patients who received conventional urophylaxis (high fluid intake, alkalinization of the urine, and the administration of diuretics) developed hematuria (>50 RBC/hpf or macrohematuria) (Morgan, Einhorn<sup>a</sup>, Costanzi). In contrast, none of the patients who received mesna injection together with this dose of ifosfamide developed hematuria (Einhorn<sup>a, b</sup>). In two

randomized studies, (Fukuoka, Scheef), higher doses of ifosfamide, from 2 to 4 g/m<sup>2</sup> administered for 3 to 5 days, produced hematuria in 31 to 100% of the patients. When mesna was administered together with these doses of ifosfamide, the incidence of hematuria was less than 7%.

Table 1 Percent of Mesna Injection Patients Developing Hematuria (≥RBC/hpf or macrohematuria)

Study	Conventional Uroprophylaxis (number of patients)	Standard Mesna Injection IV Regimen (number of patients)
<b>Uncontrolled Studies</b>		
MORGAN <sup>*</sup>	16% (7/44)	—
COSTANZI <sup>*</sup>	26% (11/43)	—
EINHORN <sup>a*</sup>	18% (7/38)	0% (0/21)
EINHORN <sup>b*</sup>	—	0% (0/32)
<b>Controlled Studies</b>		
FUKUOKA <sup>†</sup>	31% (14/46)	6% (3/46)
SCHEEF <sup>†</sup>	100% (7/7)	0% (0/8)

\*Ifosfamide dose 1.2 g/m<sup>2</sup> d x 5

†Ifosfamide dose 2 to 4 g/m<sup>2</sup> d x 3 to 5

## INDICATIONS AND USAGE

Mesna is indicated as a prophylactic agent in reducing the incidence of ifosfamide-induced hemorrhagic cystitis.

## CONTRAINDICATIONS

Mesna is contraindicated in patients known to be hypersensitive to mesna or other thiol compounds.

## WARNINGS

Allergic reactions to mesna ranging from mild hypersensitivity to systemic anaphylactic reactions have been reported. Patients with autoimmune disorders who were treated with cyclophosphamide and mesna appeared to have a higher incidence of allergic reactions. The majority of these patients received mesna orally.

Mesna has been developed as an agent to reduce the risk of ifosfamide-induced hemorrhagic cystitis. It will not prevent or alleviate any of the other adverse reactions or toxicities associated with ifosfamide therapy.

Mesna does not prevent hemorrhagic cystitis in all patients. Up to 6% of patients treated with mesna have developed hematuria (>50 RBC/hpf or WHO grade 2 and above). As a result, a morning specimen of urine should be examined for the presence of hematuria (microscopic evidence of red blood cells) each day prior to ifosfamide therapy. If hematuria develops when mesna is given with ifosfamide according to the recommended dosage schedule, depending on the severity of the hematuria, dosage reductions or discontinuation of ifosfamide therapy may be initiated.

In order to reduce the risk of hematuria, mesna must be administered with each dose of ifosfamide as outlined in the DOSAGE AND ADMINISTRATION section. Mesna is not effective in reducing the risk of hematuria due to other pathological conditions such as thrombocytopenia.

Because of the benzyl alcohol content, the multidose vial should not be used in neonates or infants and should be used with caution in older pediatric patients.

## PRECAUTIONS

### Laboratory Tests

A false positive test for urinary ketones may arise in patients treated with mesna. In this test, a red-violet color develops which, with the addition of glacial acetic acid, will return to violet.

### Drug Interactions

No clinical drug studies have been conducted.

## Carcinogenesis, Mutagenesis, Impairment of Fertility

### Carcinogenesis

No long-term animal studies have been performed to evaluate the carcinogenic potential of mesna.

### Mutagenesis

Mesna was not genotoxic in the *in vitro* Ames bacterial mutagenicity assay, the *in vitro* mammalian lymphocyte chromosomal aberration assay or the *in vivo* mouse micronucleus assay.

### Impairment of Fertility

No studies on male or female fertility were conducted. No signs of male or female reproductive organ toxicity were seen in 6-month oral rat studies (at doses up to 2000 mg/kg/day) or 29-week oral dog studies (520 mg/kg/day; both studies approximately 10-fold higher than the maximum recommended human dose on a body surface area basis).

## Pregnancy

### Teratogenic Effects: Pregnancy Category B

Reproduction studies have been performed in rats and rabbits at oral doses of 1000 mg/kg in rabbits and 2000 mg/kg in rats (approximately 10 times the maximum recommended total daily IV-oral-oral human dose on a body surface area basis) and have revealed no evidence of harm to the fetus due to mesna. There are however, no adequate and well-controlled studies in pregnant women. Because animal reproductive studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

### Nursing Mothers

It is not known whether mesna or dimesna is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for adverse reactions in nursing infants from mesna, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

### Pediatric Use

Because of the benzyl alcohol content in mesna injection, the multidose vial should not be used in neonates or infants and should be used with caution in older pediatric patients.

### Geriatric Use

Clinical studies of mesna did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy. However, the ratio of ifosfamide to mesna should remain unchanged.

## ADVERSE REACTIONS

Mesna adverse reaction data are available from four phase I studies in which single IV bolus doses of 600 to 1200 mg mesna injection without concurrent chemotherapy were administered to a total of 53 subjects.

The most frequently reported side effects (observed in two or more patients) for patients receiving single doses of mesna injection were headache, injection site reactions, flushing, dizziness, nausea, vomiting, somnolence, diarrhea, anorexia, fever, pharyngitis, hyperaesthesia, influenza-like symptoms, and coughing. In addition, constipation was reported by patients who had received repeated doses of mesna injection.

Because mesna is used in combination with ifosfamide or ifosfamide-containing chemotherapy regimens, it is difficult to distinguish the adverse reactions which may be due to mesna from those caused by the concomitantly administered cytotoxic agents.

Adverse reactions reasonably associated with mesna administered IV in four controlled studies in which patients received ifosfamide or ifosfamide-containing regimens are presented in Table 2.

Table 2 Incidence of Adverse Events and Incidence of Most Frequently Reported Adverse Events in Controlled Studies

Mesna Regimen	IV-IV-IV
N exposed	119 (100.0%)
Incidence of AEs	101 (84.9%)
Most Frequently Reported Adverse Events (Preferred Terms)	
	N (%)
Nausea	65 (54.6)
Vomiting	35 (29.4)
Constipation	28 (23.5)

Leukopenia	25 (21.0)
Fatigue	24 (20.2)
Fever	24 (20.2)
Anorexia	21 (17.6)
Thrombocytopenia	21 (17.6)
Anemia	20 (16.8)
Granulocytopenia	16 (13.4)
Asthenia	15 (12.6)
Abdominal Pain	14 (11.8)
Alopecia	12 (10.1)
Dyspnea	11 (9.2)
Chest Pain	10 (8.4)
Hypokalemia	10 (8.4)
Diarrhea	9 (7.6)
Dizziness	9 (7.6)
Headache	9 (7.6)
Pain	9 (7.6)
Sweating Increased	9 (7.6)
Back Pain	8 (6.7)
Hematuria*	8 (6.7)
Injection Site Reaction	8 (6.7)
Edema	8 (6.7)
Edema Peripheral	8 (6.7)
Somnolence	8 (6.7)
Anxiety	7 (5.9)
Confusion	7 (5.9)
Face Edema	6 (5.0)
Insomnia	6 (5.0)
Coughing	5 (4.2)
Dyspepsia	4 (3.4)
Hypotension	4 (3.4)
Pallor	4 (3.4)
Dehydration	3 (2.5)
Pneumonia	2 (1.7)
Tachycardia	1 (0.8)
Flushing	1 (0.8)

\*All grades

### Postmarketing Surveillance

Allergic reactions, decreased platelet counts associated with allergic reactions, hypertension, hypotension, increased heart rate, increased liver enzymes, injection site reactions (including pain and erythema), limb pain, malaise, myalgia, ST-segment elevation, tachycardia, and tachypnea have been reported as part of postmarketing surveillance.

### OVERDOSAGE

There is no known antidote for mesna.

### DOSAGE AND ADMINISTRATION

For the prophylaxis of ifosfamide induced hemorrhagic cystitis, mesna may be given on a fractionated dosing schedule of three bolus intravenous injections as outlined below.

### Intravenous Schedule

Mesna is given as intravenous bolus injections in a dosage equal to 20% of the ifosfamide dosage (w/w) at the time of ifosfamide administration and 4 and 8 hours after each dose of ifosfamide. The total daily dose of mesna is 60% of the ifosfamide dose. The recommended dosing schedule is outlined below:

	0 Hours	4 Hours	8 Hours
Ifosfamide	1.2 g/m <sup>2</sup>	-	-
Mesna	240 mg/m <sup>2</sup>	240 mg/m <sup>2</sup>	240 mg/m <sup>2</sup>

### Preparation of Intravenous Solutions/Stability

The mesna multidose vials may be stored and used for up to 8 days.

For IV administration the drug can be diluted by adding the Mesna Injection solution to any of the following fluids obtaining final concentrations of 20 mg mesna/mL.

- 5% Dextrose Injection, USP
- 5% Dextrose and 0.2% Sodium Chloride Injection, USP
- 5% Dextrose and 0.33% Sodium Chloride Injection, USP
- 5% Dextrose and 0.45% Sodium Chloride Injection, USP
- 0.92% Sodium Chloride Injection, USP
- Lactated Ringer's Injection, USP

For example:

One mL of Mesna Injection multidose vial 100 mg/mL may be added to 4 mL of any of the solutions listed above to create a final concentration of 20 mg mesna/mL.

Diluted solutions are chemically and physically stable for 24 hours at 25°C (77°F).

Mesna is not compatible with cisplatin or carboplatin.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

### HOW SUPPLIED

Mesna Injection is available as follows:

**NDC 55390-266-01** 1 gram; 10 mL Multidose Vial, individually boxed.

Store at 20° to 25°C (68° to 77°F). See USP for controlled room temperature.

Manufactured by:

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